Results of Testing

Chemical Name	CAS No.	Study Code/Type	Protocol/Guidline	Species	Exposure	Dose/Concentration	No. per Group	Results	Reference
Acetone	67-64-1	HENEUR Schedule Controlled Operatant Behavior	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 13-weeks	0, 1000, 2000, 4000 ppm	10/males/group	There were no treatment-related effects of acetone on clinical observations and operant performance.	62 FR 42123; 8/5/97 Docket# OPPTS-44642
n-Amyl acetate	628-63-7	HENEUR Functional Observational Battery, acute	1991 EPA Guideline EPA 540/09-01-123	rat	whole-body inhalation, 6 hr	0, 500, 1500, or 3000 ppm	10/sex/dose	No overt clinical signs of toxicity or changes in body weight, FOB evaluations were found under the conditions of this study. The NOEL was at least 3000 ppm.	62 FR 11183; 3/11/97, Docket# OPPTS-44638
n-Amyl acetate	628-63-7	HENEUR Motor Activity, acute	1991 EPA Guideline EPA 540/09-01-123	rat	whole-body inhalation, 6 hr	0, 500, 1500, or 3000 ppm	10/sex/dose	No overt clinical signs of toxicity or changes in body weight, automated motor activity measurements were found under the conditions of this study. The NOEL was at least 3000 ppm.	62 FR 11183; 3/11/97, Docket# OPPTS-44638
n-Amyl acetate	628-63-7	HENEUR Functional Observational Battery, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	whole-body inhalation 6 hr/d, 5 d/wk, 13-weeks	0, 300, 600, 1200 ppm	10/sex/group	During the first two weeks there was a reduction in activity during exposure to 600 and 1200 ppm. This effect did not persist after the end of exposure. No dose-related changes were found in FOB evaluations under the conditions of this study. For the acute sedative effects the LOEL was 600 ppm and the NOEL was 300 ppm. [EPA]	63 FR 1464, 1/9/98, Docket# OPPTS-44645
n-Amyl acetate	628-63-7	HENEUR Motor Activity, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	whole-body inhalation 6 hr/d, 5 d/wk, 13-weeks	0, 300, 600, 1200 ppm	10/sex/group	No changes in automated motor activity measurements were found under the conditions of this study. The NOEL was at least 1200 ppm. [EPA]	63 FR 1464, 1/9/98, Docket# OPPTS-44645
n-Amyl acetate	628-63-7	HENEUR Neuropathology, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	whole-body inhalation 6 hr/d, 5 d/wk, 13-weeks	0, 1200 ppm	5/sex/group	Microscopic evaluation of the brain and spinal cord from the high concentration rats revealed no morphological differences from the control rats; thus there were no compound-related changes. The NOEL was at least 1200 ppm. [EPA]	63 FR 1464, 1/9/98, Docket# OPPTS-44645
n-Butyl acetate	123-86-4	HEADME *in vivo* Hydrolysis	non-TSCA Protocol/Guideline (see docket #OPPTS-42134G)	rat (male)	intravenous	30.2 mg/kg (in 0.9% NaCl)	32	Liquid scintillation analysis following dose revealed rapid systemic distribution of the dose and very rapid elimination from the body. It was very rapidly eliminated from blood (t_{α} = 0.41 min) and was only detected in brain tissue at low concentrations in first 2.5 min after dosing. Hydrolysis in blood and brain is estimated to be 99% complete by 2.7 min at this dose level. *n*-Butanol, the hydrolysis product, was found in higher concentrations in both the blood and brain but was rapidly eliminated (t_{α} = 1.0 - 1.2 min). *n*-Buteric acid was present at low concentrations in blood and declined slowly after dosing; it was largely undetected in brain tissue.	62 FR 8955 2/27/97 Docket# OPPTS-44636

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Chemical Name	CAS No.	Study Code/Type	Protocol/Guidline	Species	Exposure	Dose/Concentration	No. per Group	Results	Reference
n-Butyl acetate	123-86-4	HENEUR Motor Activity, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs, 14 wks	0, 500, 3000, 6000 ppm	10/sex (500 and 1500 ppm), 15/sex (3000 ppm)	No spontaneous mortality occurred during the study. Exposures to n-butyl acetate vapors resulted in acute, transient signs of reduced activity levels on a daily basis at 1500 and 3000 ppm, but no evidence of a cumulative effect on activity during the 14 week exposure. There was no evidence of neurotoxicity based on motor activity. The NOEL was 3000 ppm for this study.	61 FR 11414; 3/20/96, Docket#. 44622
n-Butyl acetate	123-86-4	HENEUR Functional Obser-vational Battery, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6hrs	0, 500, 3000, 6000 ppm	10/sex/dose	Concentrations of 1500, 3000, and 6000 ppm reduced activity and response to stimulus during exposure. Sialorrhea was observed in treated male rats, but only occasionally in treated female rats. Tearing was also noted occasionally in treated female rats. No deaths were noted during exposure and no clinical signs of toxicity noted at any time post-exposure. In the Functional Observational Battery (FOB) on day 0, the hair coat scores of the 6000 ppm group were significantly higher than in controls. Forelimb grip strength for females in the 3000 ppm group was significantly higher on day 0, than for the control group. There were no differences in hair coat scores and forelimb grip strength on days 7 and 14. The differences in mean body weight between treated and control groups were less than 10%. No treatment-related gross lesions were noted at necropsy. The N0EL for changes that occurred after animals were removed from vapor was 1500 ppm.	59 FR 54193; 10/28/94, Docket# OPPTS-44613
n-Butyl acetate	123-86-4	HENEUR Schedule Controlled Operatant Behavior	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs, 13 wks	0, 500, 1500. 3000 ppm	10/sex/dose	No spontaneous mortality occurred during the study. Exposures to n-butyl acetate vapors resulted in acute, transient signs of reduced activity levels on a daily basis at 1500 and 3000 ppm in male rats, but no evidence of a cumulative effect on activity during the 13 week exposure. There was no evidence of neurotoxicity based on schedule-controlled operant behavior. The NOEL was 3000 ppm for this study.	61 FR 11414; 3/20/96, Docket#. 44622
n-Butyl acetate	123-86-4	HENEUR Motor Activity, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	0, 1500, 3000, 6000 ppm	10/sex/dose	Activity and response to stimulus were reduced during all exposure levels. Sialorrhea was observed in treated male rats, but only occasionally in treated female rats. Tearing was also noted occasionally in treated female rats. No deaths were noted during exposure and no clinical signs of toxicity noted at any time post-exposure. Mean total motor activity and total ambulations on day 0 in the 3000 and 6000 ppm groups were significantly lower than in the control group. These differences were on days 1, 7, or 14. There was no overall effect on activity during exploratory behavior or habituation periods. No treatment-related gross lesions were noted at necropsy. The N0EL for changes that occurred after animals were removed from vapor was 1500 ppm.	59 FR 54193; 10/28/94, Docket# OPPTS-44613

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Neurotoxicity

Chemical Name	CAS No.	Study Code/Type	Protocol/Guidline	Species	Exposure	Dose/Concentration	No. per Group	Results	Reference
n-Butyl acetate	123-86-4	HENEUR Neuropathology, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs, 14 wks	0, 500, 1500. 3000 ppm	10/sex (500 and 1500 ppm), 15/sex (3000 ppm)	No spontaneous mortality occurred during the study. Exposures to n-butyl acetate vapors resulted in acute, transient signs of reduced activity levels on a daily basis at 1500 and 3000 ppm, but no evidence of a cumulative effect on activity during the 14 week exposure. There was no evidence of neurotoxicity based on neuropathology. The NOEL was 3000 ppm for this study.	61 FR 11414; 3/20/96, Docket#. 44622
n-Butyl acetate	123-86-4	HENEUR Functional Obser-vational Battery, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs, 14 wks	0, 500, 1500. 3000 ppm	10/sex (500 and 1500 ppm), 15/sex (3000 ppm)	No spontaneous mortality occurred during the study. Exposures to n-butyl acetate vapors resulted in acute, transient signs of reduced activity levels on a daily basis at 1500 and 3000 ppm, but no evidence of a cumulative effect on activity during the 14 week exposure. There was no evidence of neurotoxicity based on functional observational battery tests. The NOEL was 3000 ppm for this study.	61 FR 11414; 3/20/96, Docket#. 44622
n-Butyl acetate	123-86-4	HESTOX Inhalation Probe study	Non-TSCA Protocol/ Guideline	rat	inhalation, 6 hrs/day, 2 wks	0, 750, 1500, 3000 ppm	15	Exposure of groups of 5 ad libitum-fed and 5 feed-restricted males and 5 ad libitum-fed females to test substance produced concentration-related reductions in general activity levels during exposure, but no signs of toxicity after exposure. Animals appeared to acclimate to the 750 and 1500 ppm concentrations, but not to 3000 ppm. There were no apparent differences in the clinical conditions of ad libitum-fed and feed-restricted groups during or after exposure. The 3000 ppm feed-restricted group animals lost weight during the first week of the study, while animals in all other dose groups gained weight. The NOAEL was 750 ppm for this study.	61 FR13192; 3/26/96, Docket# OPPTS-44623
Ethyl acetate	141-78-6	HENEUR Functional Obser-vational Battery, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	0, 600, 3000, 6000 ppm	14/sex/dose	No mortality was observed during the study. No overt clinical signs were noted during the exposure or observation period. Body weight loss was noted for both sexes in all dose groups on the day following exposure. Decreased absolute body weight was noted for both sexes from the 6000 ppm group following exposure. Body weight gains were observed for all exposure groups on subsequent days. Functional Observational Battery (FOB) findings were observed solely at the initial post-exposure measurement period in animals from the 3000 and 6000 ppm groups. FOB finding included drooping or closing eyelids, gait alterations, labored or audible breathing, decreased mean body temperature, hunched posture, decreased pupil size, piloerection, decreased mean forelimb grip strength, and sleeping during cageside observations. There were no gross lesions in any animal at necropsy. The NOEL for neurotoxicity was 600 ppm.	60 FR 28409; 5/31/95, Docket# OPPTS-44617

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Neurotoxicity

Chemical Name	CAS No.	Study Code/Type	Protocol/Guidline	Species	Exposure	Dose/Concentration	No. per Group	Results	Reference
Ethyl acetate	141-78-6	HENEUR Motor Activity, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	0, 600, 3000, 6000 ppm	14/sex/dose	No mortality was observed during the study. No overt clinical signs were noted during the exposure or observation period. Body weight loss was noted for both sexes in all dose groups on the day following exposure. Decreased absolute body weight was noted for both sexes from the 6000 ppm group following exposure. Body weight gains were observed for all exposure groups on subsequent days. There were no gross lesions in any animal at necropsy. The NOEL for neurotoxicity was 600 ppm.	60 FR 28409; 5/31/95, Docket# OPPTS-44617
Ethyl acetate	141-78-6	HENEUR Functional Obser-vational Battery, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk for 99-100 days	0, 350, 750, 1500 ppm	Not reported	Observations during exposure confirmed the presence of acute effects on nervous system function (diminished behavioral response to an alerting stimulus) at the 750 and 1500 ppm level. The FOB did not identify compound-related sensory or motor anomalies of toxicological relevance.	62 FR 42123; 8/5/97 Docket# OPPTS-44642
Ethyl acetate	141-78-6	HENEUR Motor Activity, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk for 99-100 days	0, 350, 750, 1500 ppm	Not reported	Observations during exposure confirmed the presence of acute effects on nervous system function (diminished behavioral response to an alerting stimulus) at the 750 and 1500 ppm level. A statistically significant reduction in motor activity (23% reduction in total duration of movements) for 1500 ppm females during test week 13. Reduction in motor activity was judged to be a non-specific manifestation of systemic toxicity.	62 FR 42123; 8/5/97 Docket# OPPTS-44642
Ethyl acetate	141-78-6	HENEUR Neuropathology, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk for 99-100 days	0, 350, 750, 1500 ppm	Not reported	Observations during exposure confirmed the presence of acute effects on nervous system function (diminished behavioral response to an alerting stimulus) at the 750 and 1500 ppm level. Neuropathological evaluation did not reveal any compound-related abnormalities. The LOEL for male rats was 350 ppm and NOEL was not demonastrated. The LOEL for female rats was 750 ppm and NOEL was 350 ppm.	62 FR 42123; 8/5/97 Docket# OPPTS-44642
Ethyl acetate	141-78-6	HENEUR Schedule Controlled Operatant Behavior	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk for 13 weeks	0, 350, 750, 1500 ppm	10/males/grou p	There were no treatment-related effects on clinical observations or performance of operant task. The NOEL was determined to be 350 ppm, this value is associated with transient acute effects of exposure. Analysis of operant behavior did not reveal any cumulative or enduring effects on performance of complex behavioral task up to 1500 ppm.	62 FR 42123; 8/5/97 Docket# OPPTS-44642

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Neurotoxicity

Chemical Name	CAS No.	Study Code/Type	Protocol/Guidline	Species	Exposure	Dose/Concentration	No. per Group	Results	Reference
Isobutyl alcohol	78-83-1	HENEUR Functional Obser-vational Battery, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	1500, 3000, 6000 ppm	10/sex/dose	Isobutanol caused a rapidly reversible general depression of the central nervous system at concentration of 3000 and 6000 ppm during the exposure period. There were no treatment-related effects in rats at the 3000 ppm concentration following exposure. Minimal effects (hypoactivity) were seen in rats at 1500 ppm during, but not after exposure. No treatment-related findings were observed in any tissue or organ during gross necropsy. The LOEL was 1500 ppm.	59 FR 60985; 11/29/94, Docket# OPPTS-44614
Isobutyl alcohol	78-83-1	HENEUR Motor Activity, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	1500, 3000, 6000 ppm	10/sex/dose	Isobutanol caused a rapidly reversible general depression of the central nervous system at concentration of 3000 and 6000 ppm during the exposure period. The transient decrease in alertness in the female rats, transient decrease in motor activity in male and female rats, and transient, slight incoordinated gait observed in one male rat were considered residual anesthetic effects at 6000 ppm. The LOEL was 1500 ppm.	59 FR 60985; 11/29/94, Docket# OPPTS-44614
Isobutyl alcohol	78-83-1	HENEUR Functional Obser-vational Battery, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 3 months	0, 250, 1000, 2500 ppm	15 (0, 2500 ppm); 10 (250, 1000 ppm)	There were no morphological or behavioral effects indicative of a persistent or progressive effect of isobutanol on the nervous system up to 2500 ppm. There were not treatment-related effects in the FOB during the study.	61 FR 17701; 4/22/96, Docket# OPPTS-44624
Isobutyl alcohol	78-83-1	HENEUR Motor Activity, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 3 months	0, 250, 1000, 2500 ppm	15 (0, 2500 ppm); 10 (250, 1000 ppm)	There were no morphological or behavioral effects indicative of a persistent or progressive effect of isobutanol on the nervous system up to 2500 ppm. There were not treatment-related effects on motor activity during the study.	61 FR 17701; 4/22/96, Docket# OPPTS-44624
Isobutyl alcohol	78-83-1	HENEUR Neuropathology, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 3 months	0, 250, 1000, 2500 ppm	20 (0, 2500 ppm); 10 (250, 1000 ppm)	There were no morphological or behavioral effects indicative of a persistent or progressive effect of isobutanol on the nervous system up to 2500 ppm. There were not treatment-related effects in neuropathology at the completion of this study. The only potential evidence of biologically significant subchronic toxicity in other organ systems was a slight increase in several hematological parameters in the 2500 female rats. A slight decrease in response to external stimuli was observed during exposure at all concentrations; this is thought to be a transient result of acute exposure to isobutanol.	61 FR 17701; 4/22/96, Docket# OPPTS-44624
Isobutyl alcohol	78-83-1	HENEUR Schedule Controlled Operatant Behavior	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 3 months	0, 250, 1000, 2500 ppm	10/sex/dose	Under the conditions of this study, there were no effects on performance under a 4 FR 20 - 2 FI 120 second schedule of food reenforcement after subchronic exposure to isobutanol at levels up to 2500 ppm.	61 FR 17701; 4/22/96, Docket# OPPTS-44624

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Neurotoxicity

Chemical Name	CAS No.	Study Code/Type	Protocol/Guidline	Species	Exposure	Dose/Concentration	No. per Group	Results	Reference
Methyl isobutyl ketone	108-10-1	HENEUR Schedule Controlled Operatant Behavior	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/day, 13 wks	0, 250, 750, 1500 ppm	10/sex/dose	Exposure to male rats to vapors of the test substance produced mild subchronic systemic effects and during exposure signs of reduced activity. However, this repeated exposure did not result in changes in Scheduled-Controlled Operant Behavior. The NOEL for subchronic neurotoxicity was 1500 ppm.	61 FR 42611; 8/16/96, Docket# OPPTS-44629
Tetrahydrofuran	109-99-9	HENEUR Functional Obser-vational Battery, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	0, 500, 2500, 5000 ppm	12/sex/dose	Transient sedation was the only effect seen at 2500 and 5000 ppm. The degree of sedation seen was concentration-dependent, and, following cessation of exposure, all test animals recovered. The NOEL was 500 ppm for this study.	61 FR 36378; 7/10/96, Docket# OPPTS-44628
Tetrahydrofuran	109-99-9	HENEUR Motor Activity, acute	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hrs	0, 500, 2500, 5000 ppm	12/sex/dose	Transient sedation was the only effect seen at 2500 and 5000 ppm. The degree of sedation seen was concentration-dependent, and, following cessation of exposure, all test animals recovered. The NOEL was 500 ppm for this study.	61 FR 36378; 7/10/96, Docket# OPPTS-44628
Tetrahydrofuran	109-99-9	HENEUR Functional Obser-vational Battery, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 90 days	0, 500, 1500, 3000 ppm	18/sex/dose	There were no biologically relevant, compound-related effects on FOB evaluation at any dose level. A diminished response to delivery of a punctate alerting stimulus at 1500 or 3000 ppm was transient and no clinical observations of comprised neurological function were detected when rats were immediately evaluated after removal from the exposure chambers. The NOEL was 500 ppm for both males and female rats based on clinical signs of sedation during exposure at 1500 and 3000 ppm.	61 FR 67334; 12/20/96, Docket# OPPTS-44635
Tetrahydrofuran	109-99-9	HENEUR Motor Activity, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 90 days	0, 500, 1500, 3000 ppm	18/sex/dose	There were no biologically relevant, compound-related effects on motor activity evaluation at any dose level. The NOEL was 500 ppm for both males and female rats based on clinical signs of sedation during exposure at 1500 and 3000 ppm.	61 FR 67334; 12/20/96, Docket# OPPTS-44635
Tetrahydrofuran	109-99-9	HENEUR Neuropathology, subchronic	1991 EPA Guideline EPA 540/09-01-123	rat	inhalation, 6 hr/d, 5 d/wk, 90 days	0, 500, 1500, 3000 ppm	18/sex/dose	There were no biologically relevant, compound-related effects on morphological endpoints observed in the neuropathology evaluation. The NOEL was 500 ppm for both males and female rats based on clinical signs of sedation during exposure at 1500 and 3000 ppm.	61 FR 67334; 12/20/96, Docket# OPPTS-44635

A T T A C H M E N T A

Neurotoxicity Testing in Proposed and Final Test Rules[2]

		Acute		Subchronic			
CAS No.	**Chemical**	**FOB**	**MA**	**FOB**	**MA**	**NP**	**SCOB**
67-64-1	Acetone	X	X	X	X	X	X
628-63-7	*n*-Amyl acetate	X	X	X	X	X	X
71-36-3	1-Butanol	X	X	X	X	X	X
123-86-4	*n*-Butyl acetate	X	X	X	X	X	X
60-29-7	Diethyl ether	X	X	X	X	X	X
110-80-5	2-Ethoxyethanol	X	X	X	X	X	X
141-78-6	Ethyl acetate	X	X	X	X	X	X
78-83-1	Isobutyl alcohol	X	X	X	X	X	X
108-10-1	Methyl isobutyl ketone (MIBK)	X	X	X	X	X	X
109-99-9	Tetrahydrofuran	X	X	X	X	X	X

[2]The test name and protocol for the tests are listed below.

Code	Test Name	Protocol
FOB	Functional observational battery	798.6050
MA	Motor activity	798.6200
NP	Neuropathology	798.6400
SCOB	Schedule-controlled operant behavior	798.6500

A T T A C H M E N T B

Neurotoxicity Testing Required Under Consent Agreement[3]

		Acute		Subchronic			
CAS No.	**Chemical**	**FOB**	**MA**	**FOB**	**MA**	**NP**	**SCOB**
67-64-1	Acetone						X
628-63-7	*n*-Amyl acetate	X	X	X	X	X	
123-86-4	*n*-Butyl acetate[4]	X	X	X	X	X	X
141-78-6	Ethyl acetate	X	X	X	X	X	X
78-83-1	Isobutyl alcohol	X	X	X	X	X	X
108-10-1	Methyl isobutyl ketone (MIBK)						X
109-99-9	Tetrahydrofuran	X	X	X	X	X	

[3]The tests shall be conducted in accordance with the 1991 EPA Guidelines in EPA 540/09-01-123, NTIS No. PB 154617. The test names are listed below.

Code	Test Name
FOB	Functional observational battery
MA	Motor activity
NP	Neuropathology
SCOB	Schedule-controlled operant behavior

[4]An *in vivo* hydrolysis test in rats after intravenous administration is also required.